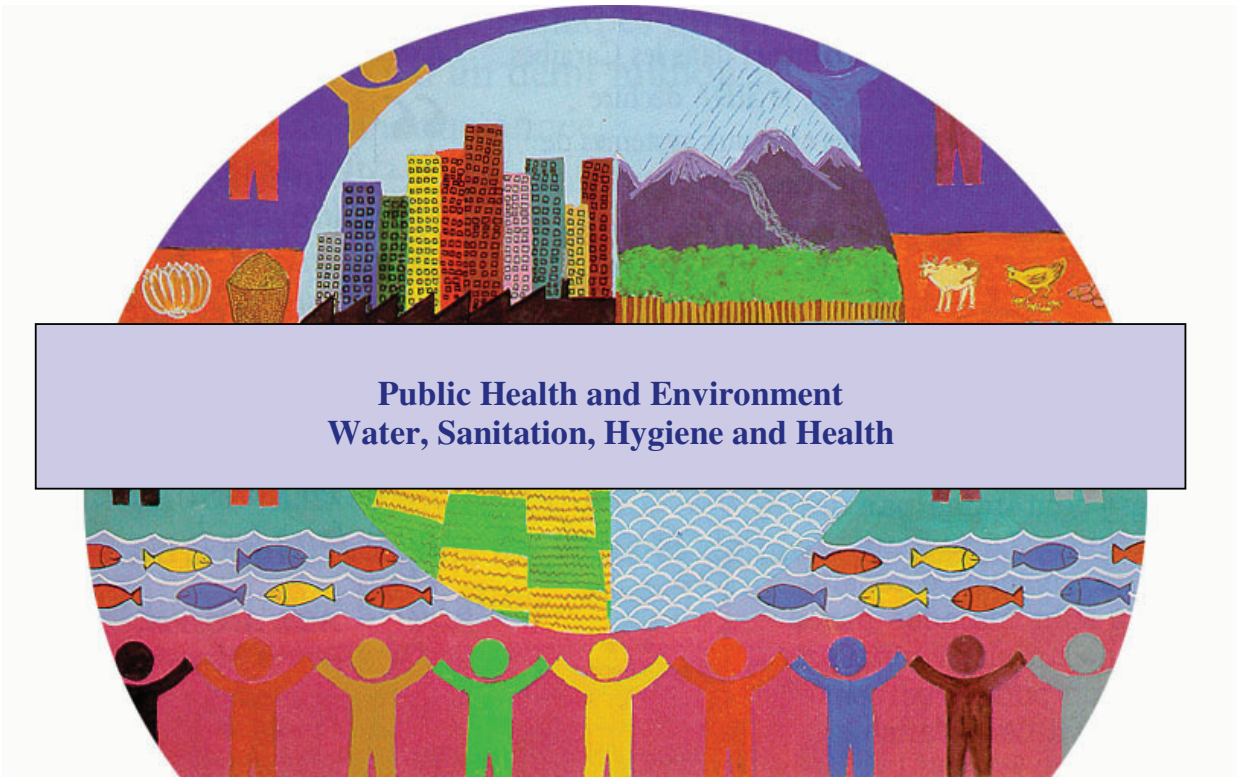
World Health Organization

Pharmaceuticals in Drinking-water



Public Health and Environment
Water, Sanitation, Hygiene and Health

WHO/HSE/WSH/11.05

Pharmaceuticals in Drinking-water

Contents

List of acronyms and abbreviations

ADI	acceptable daily intake
DWEL	drinking-water equivalent level
EDC	endocrine disrupting chemical
FAO	Food and Agriculture Organization of the United Nations
GAC	granular activated carbon
GC	gas chromatography
LC	liquid chromatography
LOAEL	lowest-observed-adverse-effect level
LOQ	limit of quantification
MF	microfiltration
MOE	margin of exposure
MS	mass spectrometry
MS/MS	tandem mass spectrometry
MTD	minimum therapeutic dose
nd	not detected
NF	nanofiltration
NOAEL	no-observed-adverse-effect level
NSAID	non-steroidal anti-inflammatory drug
PAC	powdered activated carbon
PoD	point of departure
PUB	Public Utilities Board (Singapore)
RO	reverse osmosis
SF	sand filtration
TDI	tolerable daily intake
UF	ultrafiltration
USA	United States of America
USEPA	United States Environmental Protection Agency
UV	ultraviolet
WHO	World Health Organization
WSH	Water, Sanitation, Hygiene and Health unit (WHO)

Acknowledgements

The World Health Organization (WHO) wishes to express its appreciation to all those who contributed to the preparation and development of this document through the provision of their time, expertise and experience.

WHO thanks the United States Environmental Protection Agency (USEPA) and Public Utilities Board (PUB) Singapore for their financial and technical support in developing this guidance to address an emerging issue for drinking-water.

WHO acknowledges the contributions of the members of the Working Group on Pharmaceuticals in Drinking-water, who provided important technical inputs for WHO's consideration in the development of this document. The working group members are:

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Special appreciation is extended to Mr John Fawell, independent consultant, England, who provided valuable time and technical expertise in the development of this document. Appreciation also goes to Dr Emma Goslan, Cranfield University, England, who contributed technical inputs to the chapter on the efficacy of removal of pharmaceuticals during wastewater and drinking-water treatment.

The development and production of this document were coordinated and managed by staff of the Water, Sanitation, Hygiene and Health (WSH) unit of WHO, including Mr Robert Bos (Coordinator, WSH), Mr Bruce Gordon and Mr Chee-Keong Chew (technical officers). Ms Carolyn Vickers and Dr Angelika Tritscher, WHO Headquarters, provided valuable inputs related to chemical risk assessments.

The professional editing services of Ms Marla Sheffer of Ottawa, Canada, and the secretarial support provided by Ms Penny Ward are also gratefully acknowledged.

Executive summary

Background

In the last decade, traces of pharmaceuticals, typically at levels in the nanograms to low micrograms per litre range, have been reported in the water cycle, including surface waters, wastewater, groundwater and, to a lesser extent, drinking-water. Advances in analytical technology have been a key factor driving their increased detection. Their presence in water, even at these very low concentrations, has raised concerns among stakeholders, such as drinking-water regulators, governments, water suppliers and the public, regarding the potential risks to human health from exposure to traces of pharmaceuticals via drinking-water.

Following requests from several Member States for information regarding the potential health impacts of residual concentrations of pharmaceuticals in drinking-water, this issue was added to the work plan of the World Health Organization (WHO) Drinking-water Quality Committee in 2005. It was proposed that a working group of experts be assembled to undertake a rapid review of the state of the science of pharmaceuticals in drinking-water and develop guidance and recommendations in a report and fact sheet.

A WHO working group that comprised experts in toxicology, water chemistry, water quality and health, water treatment, pharmacology, and drinking-water regulation and policy was formed in 2009. Consultations were held in 2009 and 2010 with the Drinking-water Quality Committee and additional experts to review and summarize the available scientific knowledge and evidence.

A literature review was a key source of evidence. This examined the fate and occurrence of pharmaceuticals in water, exposure to pharmaceuticals in drinking-water, assessment of the human health risk associated with pharmaceuticals in drinking-water, removal of pharmaceuticals during wastewater and drinking-water treatment, and preventive management measures to reduce potential exposure to pharmaceuticals in drinking-water.

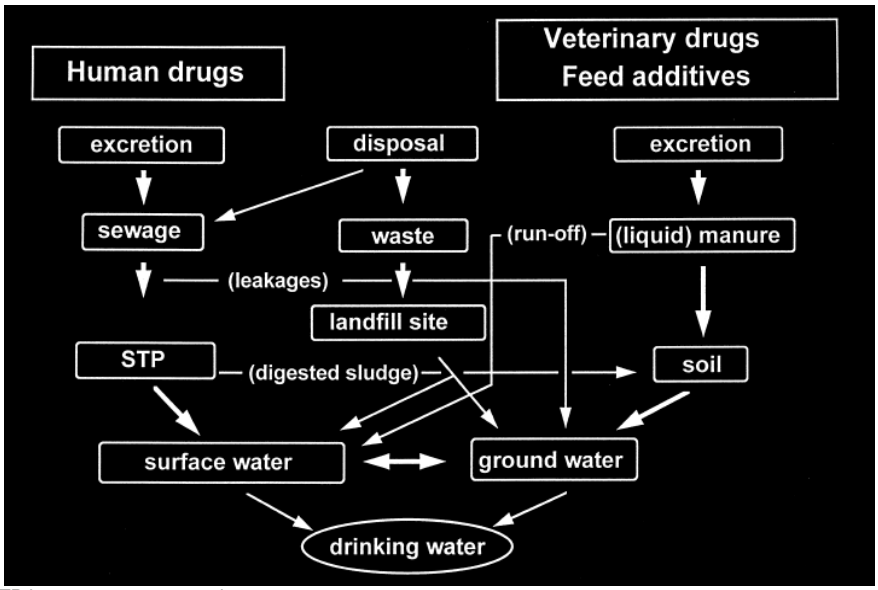
This report contains the key findings and recommendations of the working group and consultations with experts in the Drinking Water Quality Committee. It aims to provide practical guidance and recommendations for managing the emerging concern about pharmaceuticals in drinking-water, taking into consideration the evidence from the literature review. More importantly, it emphasizes the need to prioritize this emerging issue in the overall context of water safety management, which includes microbial and other chemical risks that may threaten the safety of drinking-water.

Scope

This report focuses primarily on reviewing the risks to human health associated with exposure to trace concentrations of pharmaceuticals in drinking-water. It does not discuss the potential impacts on aquatic ecosystems or the broader physical environment.

Occurrence of pharmaceuticals in water

Pharmaceuticals are synthetic or natural chemicals that can be found in prescription medicines, over-the-counter therapeutic drugs and veterinary drugs. Pharmaceuticals contain active ingredients that have been designed to have pharmacological effects and confer significant benefits to society. The occurrence of pharmaceuticals in the environment and the water cycle at trace levels (in the range of nanograms to low micrograms per litre) has been widely discussed and published in literature in the past decade. The increase in detection is largely attributable to the advances in analytical techniques and instrumentation. Many surveys and studies have confirmed the presence of pharmaceuticals in municipal wastewater and effluents, and these have been identified as a major source of pharmaceuticals in drinking-water (Figure ES1).



Note: STP is sewage treatment plant.

Figure ES1: Fate and transport of pharmaceuticals in the environment (Ternes, 1998)

Routine monitoring programmes to test drinking-water for pharmaceuticals have not been implemented, as is the case for regulated chemical and microbial parameters. Generally, data on the occurrence of pharmaceuticals in drinking-water have resulted from ad hoc surveys or targeted research projects and investigations. Available studies have reported that concentrations of pharmaceuticals in surface waters, groundwater and partially treated water are typically less than 0.1 µg/l (or 100 ng/l), and concentrations in treated water are generally below 0.05 µg/l (or 50 ng/l).

More systematic studies will help to further our understanding of the transport, occurrence and fate of pharmaceuticals in the environment, especially drinking-water sources. Standardization of protocols for sampling and analysing pharmaceuticals would help to facilitate the comparison of data.

Human health risk assessment for pharmaceuticals in drinking-water

Pharmaceuticals are normally governed by stringent regulatory processes and require rigorous preclinical and clinical studies to assess their efficacy and safety before

commercialization. Therefore, pharmaceuticals are generally better characterized than other environmental contaminants.

This report reviews human health risk assessments of pharmaceuticals in drinking-water conducted in the United Kingdom, Australia and the United States of America (USA). The approaches of acceptable daily intake (ADI) or minimum therapeutic dose (MTD) were adopted as the point of departure in these studies to assess potential risks to human health through exposure to pharmaceuticals in drinking-water. Margins of exposure (MOEs) were derived by comparing measured or modelled exposure levels in drinking-water with a reference exposure concentration, which was usually the ADI or MTD or sometimes a drinking-water equivalent level (DWEL). A judgement of safety could then be based on the magnitude of this MOE for the pharmaceutical under consideration. In other words, screening values to determine whether further action is warranted could be derived from the ADI or the MTD, with uncertainty factors applied as appropriate.

Analysis of the results indicated that appreciable adverse health impacts to humans are very unlikely from exposure to the trace concentrations of pharmaceuticals that could potentially be found in drinking-water. Concentrations of pharmaceuticals in drinking-water are generally more than 1000-fold below the MTD, which is the lowest clinically active dosage. The findings from these three case-studies are in line with the evidence published over the past decade, which suggests that appreciable risks to health arising from exposure to trace levels of pharmaceuticals in drinking-water are extremely unlikely.

Treatment technologies for removal of pharmaceuticals from drinking-water

Having established that raw sewage and wastewater effluents are a major source of pharmaceuticals found in surface waters and drinking-water, it is important to consider and characterize the efficiency of processes for the removal of pharmaceuticals during wastewater and drinking-water treatment. Most of the research has been conducted at the laboratory scale or at full scale in developed countries, including the USA, Japan, the Republic of Korea and countries in Europe.

Even though wastewater and drinking-water treatment processes are not designed specifically to remove pharmaceuticals, they may do so to varying degrees. Pharmaceuticals are not “unusual” chemicals; their removal efficiencies during wastewater and drinking-water treatment are dependent on their physical and chemical properties. In cases where regulations require controls to mitigate risks from exposure to pesticides, treatment barriers may already be optimized to remove pharmaceuticals.

Conventional wastewater treatment facilities generally have activated sludge processes or other forms of biological treatment such as biofiltration. These processes have demonstrated varying removal rates for pharmaceuticals, ranging from less than 20% to greater than 90%. The efficiency of these processes for the removal of pharmaceuticals varies within and between studies and is dependent on operational configuration of the wastewater treatment facility. Factors influencing removal include sludge age, activated sludge tank temperature and hydraulic retention time.

Comparatively, advanced wastewater treatment processes, such as reverse osmosis, ozonation and advanced oxidation technologies, can achieve higher removal rates for pharmaceuticals.

Studies on conventional drinking-water treatment processes have shown that coagulation is largely ineffective in removing pharmaceuticals. Free chlorine is able to remove up to approximately 50% of the pharmaceuticals investigated, whereas chloramines have lower removal efficiency. Compounds that showed high removal by free chlorine but low removal by chloramines include antibiotics, such as sulfamethoxazole, trimethroprim and erythromycin.

Advanced water treatment processes, such as ozonation, advanced oxidation, activated carbon and membranes (e.g. nanofiltration, reverse osmosis), are able to achieve higher removal rates (above 99%) for targeted pharmaceutical compounds in various studies in the published literature.

Advanced and costly water treatment technology will not be able to completely remove all pharmaceuticals to concentrations less than the detection limits of the most sensitive analytical procedures at all times. Therefore, it is imperative that the toxicological relevance of various compounds be considered in the context of appreciable risks to human health. An informed risk assessment is essential before scarce resources are allocated to upgrade or invest in additional advanced treatment processes to reduce trace concentrations of pharmaceuticals in drinking-water.

Preventing pharmaceuticals in drinking-water

Conventional drinking-water quality monitoring that focuses on end-product testing is resource intensive in terms of capital investment and human resources. Coupled with an expanding list of chemical contaminants in drinking-water and water sources that may be of insignificant health concern, an overemphasis on end-product monitoring and the upgrading of treatment infrastructure is not a sustainable, optimal use of limited resources.

As outlined in the WHO *Guidelines for Drinking-water Quality*, the water safety plan approach is "the most effective means of consistently ensuring the safety of a drinking-water supply … through the use of a comprehensive risk assessment and risk management approach that encompasses all steps in the water supply from catchment to consumer". Water safety plans highlight the importance of considering risk assessment and risk management comprehensively from source to tap and adopting preventive measures to address the source of risks.

Adapting the water safety plan approach to the context of pharmaceuticals in drinking-water means that preventing pharmaceuticals from entering the water supply cycle during their production, consumption (i.e. excretion) and disposal is a pragmatic and effective means of risk management. Preventive measures need to be applied as close as possible to the source of the risk and hazard.

Inappropriate disposal practices, such as flushing unwanted or excess drugs down toilets and sinks and discarding them into household waste, are common and may be

the main contributors to pharmaceuticals in wastewater and other environmental media, such as surface waters and landfill leachate.

Preventive measures, such as policies promoting or regulations governing disposal practices at concentrated point sources (e.g. health-care and veterinary facilities), can reduce the amount of pharmaceutical waste entering water bodies. In addition, take-back programmes, guidance and enhanced consumer education will support efforts for the proper disposal of medicines and reduce the impact of pharmaceuticals entering our water sources.

Conclusions

Published literature and national studies have shown that concentrations of pharmaceuticals in surface water and groundwater sources impacted by wastewater discharges are typically less than 0.1 µg/l (or 100 ng/l), and concentrations in treated drinking-water are usually well below 0.05 µg/l (or 50 ng/l). There are few comprehensive, systematic studies on the occurrence of pharmaceuticals in drinking-water. Limited data on the occurrence of pharmaceuticals in drinking-water are a challenge in assessing potential human health risks from exposure to trace concentrations of pharmaceuticals in drinking-water.

Several approaches to screen and prioritize pharmaceuticals have been published in peer-reviewed literature. These approaches usually apply the principles of the point of departure to derive a margin of exposure between the reported worst-case exposure and the MTD, the ADI or sometimes the DWEL.

Targeted investigations conducted in the United Kingdom, the USA and Australia found that pharmaceuticals are largely present in drinking-water at concentrations several orders of magnitude (more than 1000-fold) below the minimum therapeutic dose and largely below the calculated ADIs and DWELs. The substantial margins of safety for individual compounds suggest that appreciable adverse impacts on human health are very unlikely at current levels of exposure in drinking-water.

From a treatment perspective, pharmaceuticals are not unusual organic chemicals, and treatment removal rates depend on the physical and chemical properties of the compounds. Conventional treatment processes with chlorination (free chlorine) can remove about 50% of these compounds, whereas advanced treatment processes, such as ozonation, advanced oxidation, activated carbon and membranes (e.g. reverse osmosis, nanofiltration), can achieve higher removal rates; reverse osmosis, for example, can remove more than 99% of large pharmaceutical molecules.

Recommendations

Trace quantities of pharmaceuticals in drinking-water are very unlikely to pose risks to human health because of the substantial margin of exposure or margin of safety between the concentrations detected and the concentrations likely to evoke a pharmacological effect.

Concerns over pharmaceuticals should not divert the attention and valuable resources of water suppliers and regulators from the various bacterial, viral and protozoan waterborne pathogens and other chemical priorities, such as lead and arsenic.

The current levels of exposure to pharmaceuticals in drinking-water also suggest that the development of formal guideline values for pharmaceuticals in the WHO *Guidelines for Drinking-water Quality* is unwarranted.

Routine monitoring of pharmaceuticals in water sources and drinking-water at the national level and the installation of specialized drinking-water treatment infrastructure to reduce the very low concentrations of pharmaceuticals in drinking-water are not currently deemed necessary given the limited additional health benefits. However, where specific circumstances, such as a catchment survey, indicate a potential for elevated concentrations of pharmaceuticals in the water cycle (surface water, groundwater, wastewater effluent and drinking-water), relevant stakeholders could undertake targeted, well-designed and quality-controlled investigative studies to obtain more information to assess potential health risks arising from exposure through drinking-water. If necessary, screening values could be developed and an assessment of the need for treatment enhancement could also be considered within the context of other risks and priorities using the water safety plan.

Human exposure to pharmaceuticals through drinking-water can be reduced through a combination of preventive measures, such as take-back programmes, regulations, public guidance and consumer education to encourage the proper disposal of unwanted pharmaceuticals and minimize the introduction of pharmaceuticals into the environment.

Enhanced risk communication to the public and public education efforts on water quality issues from the human health standpoint will help the public to better understand this issue relative to other hazards, such as pathogenic microbial risks. This means conveying the risks of exposure to very low concentrations of pharmaceuticals in drinking-water to the public using plain language.

Knowledge gaps and future research

Although current published risk assessments indicate that trace concentrations of pharmaceuticals in drinking-water are very unlikely to pose risks to human health, knowledge gaps exist in terms of assessing risks associated with long-term exposure to low concentrations of pharmaceuticals and the combined effects of mixtures of pharmaceuticals.

Future research in these areas may be beneficial to better characterize potential health risks from long-term, low-level exposure to pharmaceuticals, particularly for sensitive subpopulations.

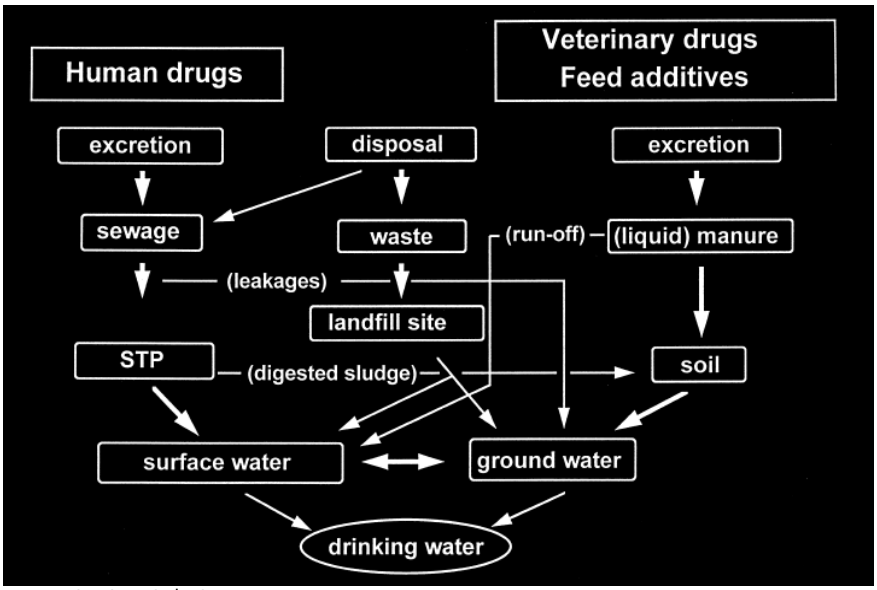
One of the key challenges in estimating exposures to pharmaceuticals in drinking-water and assessing the potential risks to human health is the limited occurrence data for such a diverse group of human and veterinary pharmaceuticals. Implementing monitoring programmes is resource intensive in terms of costs, human resources and infrastructure, and there is also a lack of standardized sampling and analysis protocols

to support monitoring studies. Future research should focus on filling these knowledge gaps, including by providing support to practitioners through the development of cost-effective methods and protocols for prioritizing pharmaceuticals within the context of an overall risk assessment for all drinking-water hazards.

Noting that pharmaceuticals in drinking-water are an emerging issue, WHO will continue to review relevant scientific evidence and, where necessary, update the guidance provided in this report.

1. Occurrence of pharmaceuticals in water

Pharmaceuticals are synthetic or natural chemicals that can be found in prescription medicines, over-the-counter therapeutic drugs and veterinary drugs, and they contain active ingredients that evoke pharmacological effects and confer significant benefits to society. The ubiquitous use of pharmaceuticals in human and veterinary medical practices, aquaculture and agricultural products has led to the continual release of a wide array of pharmaceutical chemicals into our environment. As illustrated in Figure 1, pharmaceuticals enter the environment through many routes, including human or animal excreta, wastewater effluent, treated sewage sludge, industrial waste, medical waste from health-care and veterinary facilities, landfill leachate and biosolids.



Note: STP is sewage treatment plant.

Figure 1: Fate of pharmaceuticals in the environment (Ternes, 1998)

Pharmaceuticals and their metabolites undergo natural attenuation by adsorption, dilution or degradation in the environment, depending on their hydrophobicity and biodegradability and on the temperature. Therefore, pharmaceuticals in water sources and drinking-water are often present at trace concentrations, as these compounds would have undergone metabolism and removal through natural processes and, if applicable, wastewater and drinking-water treatment processes.

1.1 Advances in analytical and detection methods

The increase in reported detections of very low concentrations of pharmaceuticals in various environmental matrices, including the water cycle (e.g. surface water, groundwater, treated wastewater effluent and drinking-water), is mainly attributable to technological advances in the sensitivity and accuracy of detection equipment and analytical methods. Gas chromatography with mass spectrometry (GC-MS) or tandem mass spectrometry (GC-MS/MS) and liquid chromatography with mass spectrometry

(LC-MS) or tandem mass spectrometry (LC-MS/MS)[1] are advanced methods that are able to determine target compounds to the nanogram per litre level and are commonly applied for the detection of pharmaceutical compounds in water and wastewater. The selection of methods is dependent on the physical and chemical properties of the target compound. LC-MS/MS analysis is more suitable for measuring target compounds that are more polar and highly soluble in water, whereas GC-MS/MS is better for more volatile target compounds. Figure 2 provides examples of pharmaceuticals in water and wastewater that can be detected using these advanced analytical methods (Fatta et al., 2007).

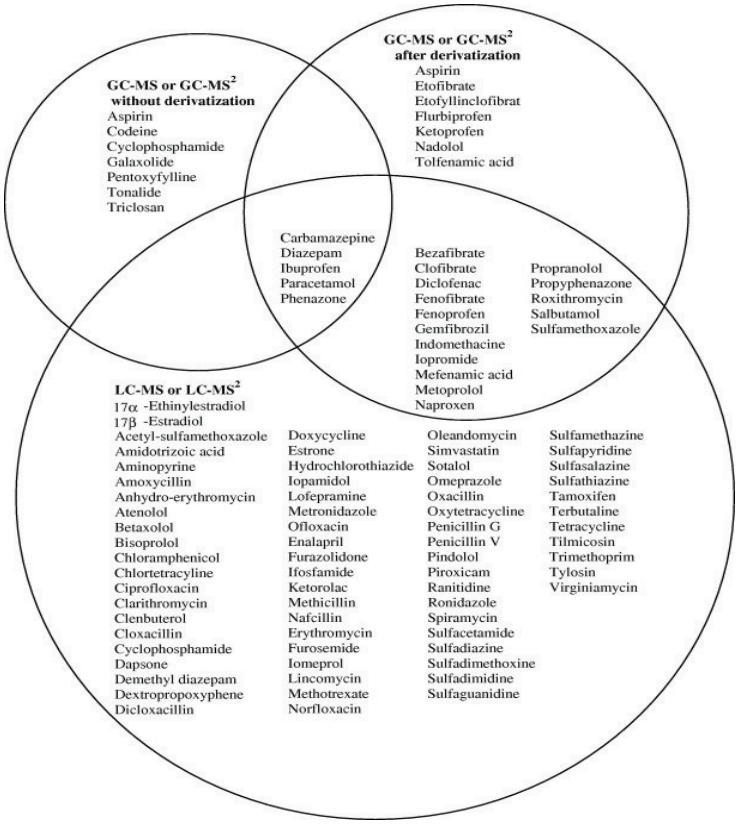


Figure 2. An illustration of analytical methods applied to detect pharmaceuticals in water and wastewater (Fatta et al., 2007)

Whereas improved detection and analytical capabilities will allow us to learn more about the fate and occurrence of pharmaceutical chemicals in the environment, including the water cycle, it is important to recognize that detection of these compounds does not directly correlate to human health risks that could be verified by available human risk assessment methods. In addition, there is currently no standardized practice or protocol for the sampling and analytical determination of pharmaceuticals in water or any other environmental media that ensures the comparability and quality of the data generated.

[1] GC-MS/MS and LC-MS/MS refer to GC-MS² and LC-MS², respectively, in Figure 2.

1.2 Occurrence of pharmaceuticals in surface water

Scientists demonstrated the presence of pharmaceuticals in the environment more than 30 years ago, with studies in the United States of America (USA) in the 1970s that reported the presence of heart medications, pain relievers and birth control medications in wastewater (Tabak & Bunch, 1970; Garrison, Pope & Allen, 1976; Hignite & Azarnoff, 1977). The most cited reference in the peer-reviewed literature on the occurrence of pharmaceuticals in surface waters is the survey by the United States Geological Survey, in which more than 50 pharmaceuticals in 139 streams across 30 states in USA were investigated during 1999 and 2000 (Kolpin et al., 2002).

Many peer-reviewed and published studies have shown that the primary sources of pharmaceuticals entering surface water are from excretion and bathing through treated or untreated municipal wastewater effluent discharges into receiving surface water bodies (Buser, Muller & Theobald, 1998; Ternes, 1998; Buser, Poiger & Muller, 1999; Daughton & Ternes, 1999; Daughton, 2001; Heberer et al., 2001; Heberer, Reddersen & Mechlinski, 2002; Kolpin et al., 2002) and improper disposal of pharmaceutical waste and excess medication by consumers and health-care and veterinary facilities into sewers and drains. Table 1 illustrates several classes of pharmaceuticals found in wastewater influent in a study conducted by the Drinking Water Inspectorate in the United Kingdom.

Table 1. Excretion rates of unmetabolized active ingredients for selected pharmaceuticals

Compound	Pharmaceutical product group	Parent compound excreted (%)	Reference
Amoxycillin	Antibiotic	60	Bound & Voulvoulis (2005)
Atenolol	Beta blocker	90	Bound & Voulvoulis (2005)
Bezafibrate	Lipid regulator	50	Bound & Voulvoulis (2005)
Carbamazepine	Antiepileptic	3	Bound & Voulvoulis (2005)
Cetirizine	Antihistamine	50	Bound & Voulvoulis (2005)
Clofibric acid	Active metabolite	6	Alder et al. (2006)
Diclofenac	Anti-inflammatory	15	Alder et al. (2006)
Erythromycin	Antibiotic	25	Bound & Voulvoulis (2005)
Felbamate	Antiepileptic	40–50	Bound & Voulvoulis (2005)
Ibuprofen	Analgesic	10	Bound & Voulvoulis (2005)

Source: DWI (2007)

A monitoring programme in the United Kingdom focused on 12 pharmaceutical compounds or their metabolites in surface waters (Ashton, Hilton & Thomas, 2004). The results showed that a range of pharmaceuticals from different therapeutic classes were present in both effluents from sewage treatment works and receiving waters in England. The values reported were within the same range as those reported in continental Europe and the USA, where more extensive monitoring has been conducted. Results in the published literature for studies conducted in the USA and Europe also suggest that usage data are positively associated with concentrations of pharmaceuticals measured in effluent and in surface water bodies receiving the treated effluent. Tables 2 and 3 show additional illustrative examples of pharmaceuticals that have been found in the United Kingdom and other European countries, respectively.

Table 2. Measured concentrations of selected pharmaceuticals in the aquatic environment in the United Kingdom

Compound	Median (maximum) concentration (ng/l)		References
	Sewage treatment works effluent	Stream or river waters	
Bleomycin	11 (19)	nd (17)	Aherne, Hardcastle & Nield (1990)
Clotrimazole	14 (27)	21 (34)	Roberts & Thomas (2006)
	—	7 (22)	Thomas & Hilton (2004)
Diclofenac	424 (2349)	< LOQ (568)	Ashton, Hilton & Thomas (2004)
	289 (598)	< LOQ	Roberts & Thomas (2006)
	—	< LOQ (195)	Thomas & Hilton (2004)
Dextropropoxyphene	195 (585)	58 (682)	Ashton, Hilton & Thomas (2004)
	37 (64)	12 (98)	Roberts & Thomas (2006)
Erythromycin	—	< LOQ (80)	Thomas & Hilton (2004)
	< LOQ (1842)	< LOQ (1022)	Ashton, Hilton & Thomas (2004)
Fluoxetine	202 (290)	5 (70)	Roberts & Thomas (2006)
	7.6–52.9	2–43.7	Boucard & Gravell (2006)
Ibuprofen	3086 (27 256)	826 (5044)	Ashton, Hilton & Thomas (2004)
	2972 (4239)	297 (2370)	Roberts & Thomas (2006)
	—	48 (930)	Thomas & Hilton (2004)
Mefenamic acid	133 (1440)	62 (366)	Ashton, Hilton & Thomas (2004)
	340 (396)	< LOQ	Roberts & Thomas (2006)
	—	< LOQ (196)	Thomas & Hilton (2004)
Norfluoxetine	5.2–30.7	4.5–83.0	Boucard & Gravell (2006)
Paracetamol	< 20	—	Roberts & Thomas (2006)
	—	555	Bound & Voulvoulis (2006)
Propanolol	76 (284)	29 (215)	Ashton, Hilton & Thomas (2004)
	304 (373)	61 (107)	Roberts & Thomas (2006)
	—	< LOQ (56)	Thomas & Hilton (2004)
Sulfamethoxazole	< LOQ (132)	< LOQ	Ashton, Hilton & Thomas (2004)
Tamoxifen	< LOQ (42)	< LOQ	Ashton, Hilton & Thomas (2004)
Tetracycline	—	~1000	Watts et al. (1983)
Theophylline	—	~1000	Watts et al. (1983)
Trimethoprim	70 (1288)	< LOQ (42)	Ashton, Hilton & Thomas (2004)
	271 (322)	9 (19)	Roberts & Thomas (2006)
	—	7 (569)	Thomas & Hilton (2004)

LOQ, limit of quantification; nd, not detected (below the detection limit)
Source: DWI (2007)

Table 3. Concentrations of selected pharmaceuticals found in European surface waters

Compound	Median (maximum) concentrations (ng/l)				
	Austria	Finland	France	Germany	Switzerland
Bezafibrate	20 (160)	5 (25)	102 (430)	350 (3100)	—
Carbamazepine	75 (294)	70 (370)	78 (800)	25 (110)	30–150
Diclofenac	20 (64)	15 (40)	18 (41)	150 (1200)	20–150
Ibuprofen	nd	10 (65)	23 (120)	70 (530)	nd (150)
Iopromide	91 (211)	—	7 (17)	100 (910)	—
Roxithromycin	nd	—	9 (37)	< LOQ (560)	—
Sulfamethoxazole[a]	nd	—	25 (133)	30 (480)	—

LOQ, limit of quantification; nd, not detected (below the detection limit)

[a] Includes the human metabolite N^4-acetyl-sulfamethoxazole.

Source: Ternes et al. (2005)

1.3 Occurrence of pharmaceuticals in drinking-water

Most countries (if any) do not have monitoring programmes to routinely test for pharmaceuticals in drinking-water owing to practical difficulties, such as high costs and lack of availability of routine analytical technologies and laboratory infrastructure to detect a diverse range of pharmaceuticals and their metabolites. As a result, the majority of the occurrence data for pharmaceuticals in drinking-water and surface waters come from targeted research projects, targeted investigations and ad hoc surveys, most of which were designed to develop, test and fine-tune detection and analytical methods. Nevertheless, they did provide an initial indication of the presence of pharmaceuticals in the environment.

Studies in the USA have detected very low levels of pharmaceuticals in finished drinking-water. The highest concentration reported was 40 ng/l for meprobamate (Benotti et al., 2009). Studies have also found several pharmaceuticals in tap water at concentrations ranging from nanograms to low micrograms per litre in several countries in Europe, including Germany, the Netherlands and Italy (Huerta-Fontela, Galceran & Ventura, 2011). Two separate studies in Germany (Reddersen, Heberer & Dünnbier, 2002; Zühlke et al., 2004) found phenazone and propylphenazone (an analgesic and an antipyretic drug, respectively) in Berlin drinking-water, with the highest concentration being 400 ng/l for phenazone. This high value was largely attributed to groundwater, used as a drinking-water source, contaminated with sewage (Jones, Lester & Voulvoulis, 2005). In the Netherlands, traces of antibiotics, antiepileptics and beta blockers were detected in the drinking-water supply at concentrations below 100 ng/l, with most concentrations below 50 ng/l (Mons, Hoogenboom & Noij, 2003).

To date, between 15 and 25 pharmaceuticals have been detected in treated drinking-water worldwide, as reported in the peer-reviewed scientific literature (Jones, Lester & Voulvoulis, 2005; Benotti et al., 2009). More pharmaceutical compounds have been detected in untreated water sources, such as wastewater, surface waters and groundwaters (Focazio et al., 2008) in the water cycle, largely attributable to pharmaceuticals of very high usage, including antihyperlipidaemic compounds and non-steroidal anti-inflammatory drugs (NSAIDs).

1.4 Conclusion

The occurrence of pharmaceuticals in the environment, including the water cycle, at concentrations ranging from nanograms to low micrograms per litre has been widely discussed and published in the literature in the past decade (Heberer, Schmidt-Bäumler & Stan, 1998; Zuccato et al., 2000; Heberer, Fuhrmann, Schmidt-Baumier, Tsipi, Koutsouba & Hiski, 2001; Heberer et al., 2004; Stackelberg et al., 2004, 2007; Zühlke et al., 2004; Jones, Lester & Voulvoulis, 2005; Vieno, Tuhkanen & Kronberg, 2005; Loraine et al., 2006; Loraine & Pettigrove, 2006; Snyder et al., 2006; Vanderford & Snyder, 2006; Loos et al., 2007; Pérez & Barceló, 2007; Togola & Budzinski, 2008; Mompelat, Le Bot & Thomas, 2009).

The published literature and national studies have shown that concentrations of pharmaceuticals in surface water and groundwater sources impacted by wastewater discharges are typically less than 0.1 µg/l (or 100 ng/l), and concentrations in treated drinking-water are usually well below 0.05 µg/l (or 50 ng/l).

There are few comprehensive, systematic monitoring studies on pharmaceuticals in drinking-water, and limited occurrence data are a challenge in assessing potential human health risks from exposure to trace concentrations of pharmaceuticals in drinking-water. In addition, there is no standardized protocol for the sampling and analytical determination of pharmaceuticals. More systematic studies, using comparable methods, will help further research on the transport, occurrence and fate of these compounds in various environmental media, and standardization of protocols for their sampling and analytical determination would help to facilitate the comparison of data.

2. Human health risk assessment for pharmaceuticals in drinking-water

2.1 Introduction

Regulatory approval processes for pharmaceuticals require thorough assessments to demonstrate the efficacy and safety of active compounds. These assessments determine the margin of safety associated with human consumption and take into account the risk–benefit equation. Those pharmaceuticals that are most widely used, particularly those approved for over-the-counter sales, require the most stringent assessment and require a substantial margin of safety. Most of the pharmaceuticals that are likely to be found in water fall into the high usage category, because it is those substances that will be present in the greatest quantity. The assessments for approval for particular uses cover a series of preclinical, clinical and sometimes mechanistic studies and are usually performed at doses close to the intended therapeutic dose. For those substances that will be widely used, some studies are also conducted at doses well above those anticipated. Because of these stringent regulatory approval processes, pharmaceuticals will be better characterized and controlled than most environmental contaminants.

Concern has been raised, however, because exposure to pharmaceuticals through drinking-water is an unintended and involuntary exposure over potentially long periods of time. Moreover, there are few scientific risk assessments of exposure to low levels of pharmaceuticals, both as individual species or as mixtures, in drinking-water.

2.2 Assessing risks associated with pharmaceuticals in drinking-water

Chemical risk assessment methods for substances found in food and drinking-water involve establishing an acceptable daily intake (ADI) or tolerable daily intake (TDI) based on a variety of calculations (e.g. from extrapolations, applications of uncertainty factors) applied to a selected point of departure (PoD) from the toxicological and epidemiological database. A common and widely accepted PoD is that concentration at which no adverse effects are detected, which is the no-observed-adverse-effect level (NOAEL), or, less optimally, the lowest concentration at which adverse effects are detected, which is the lowest-observed-adverse-effect level (LOAEL), in combination with an additional uncertainty factor. The PoD may also be derived through a benchmark dose based on statistical evaluation of the dose–response curve of the critical study (FAO/WHO, 2009).

Health risks from pharmaceuticals in water have been most frequently assessed using the minimum therapeutic dose (MTD, the lowest concentration that evokes a desired therapeutic effect among target populations) as the PoD (DWI, 2007; Bull et al., 2011). This is due to practical reasons, including the lack of readily available toxicological data in the public domain that would be necessary to derive a NOAEL/LOAEL or benchmark dose. The MTD is usually a dose below those concentrations where, in rare instances, unacceptable adverse or toxic effects are observed. Therefore, the use of the MTD as a PoD for risk assessment would often result in the development of conservative screening values (reference concentrations used to determine whether further action is warranted, as described below).

The application of the MTD to inform the derivation of screening values does present certain limitations. The MTD is determined by controlled studies in specific preselected populations, which may not be based on the sensitivities of vulnerable subpopulations that would not normally be given the drug. In addition, in specific cases, such as with cytotoxic cancer treatment drugs, the MTD may be at a concentration above which toxic effects are observed. Notwithstanding this, especially in cases where the margins of exposure (MOEs) are substantial, use of the MTD could be considered a pragmatic and sensible method to broadly assess and screen risks.

The main challenges in assessing risks include the limited occurrence data available for pharmaceuticals in drinking-water, the diverse range of pharmaceuticals in use, the wide variation in the use of individual pharmaceuticals between countries, the limited number of data in the public domain and technical limitations relating to assessing risks from chronic exposure to low-dose of pharmaceuticals and mixtures. Nonetheless, several publicly available approaches (USEPA, 2008b) have been used for screening and prioritizing pharmaceuticals for assessing the potential risks to human health from exposure to low concentrations of pharmaceuticals in drinking-water. These reports (DWI, 2007; USEPA, 2008b; Bull et al., 2011) have been subject to scrutiny and peer review. These studies have used the MTD as the PoD for the risk assessment, with subsequent application of uncertainty factors to derive screening values and margins of safety against which to assess the potential risk

These screening values are values against which to judge the likelihood that a particular substance could be of concern at the concentrations observed and so warrant further, more detailed investigation. Screening values are also used to identify those substances from a long list that are the most important and should be considered more closely. As indicated above, there are two approaches that have been used. An ADI or TDI is an amount that can be ingested daily for an extended period, generally a lifetime, without significant risk to health. The large uncertainty factors frequently involved in establishing an ADI or TDI generally serve to provide assurance that exposure exceeding the ADI or TDI for shorter periods, or sometimes for longer periods if the exceedance is small, is unlikely to have any deleterious effect. However, any exceedance of the ADI or TDI needs to be evaluated on a case-by-case basis, as it is very much dependent on the substance and its toxicological profile.

ADIs are typically set by determining the dose at which no adverse effect is observed (the NOAEL) or, less optimally, the lowest level at which an adverse effect is observed (the LOAEL). In both cases, uncertainty factors are applied to reflect uncertainties in extrapolation from experimental animals to humans, in the likely variation within the exposed population or important gaps in the database, to derive the ADI. These uncertainty factors are based on expert judgement, but there is a considerable body of experience in their use. Data from well-conducted studies, where a clear dose–response relationship has been demonstrated, are preferred, typically using experimental animal models; however, where suitable data on human populations are available, these would normally be preferred. The approaches used in developing guideline or screening values for chemicals in drinking-water are described in chapter 8 of the WHO *Guidelines for Drinking-water Quality* (WHO, 2011). Using an ADI to determine a suitable level for drinking-water requires assumptions to be made regarding body weight, as an ADI is usually presented as an

intake per kilogram of body weight. WHO uses a value of 60 kg for an adult and assumes consumption of 2 litres of drinking-water per day. Usually for substances for which an ADI is derived, exposure can also be from food and air, and so a proportion of the ADI is allocated to drinking-water to allow for exposure from other sources. In the case of pharmaceuticals, exposure from other sources is negligible, and so the allocation can be high, even 100%. For individuals taking the pharmaceutical for medical purposes, the additional amount from drinking-water is so small as to make no difference.

The MTD, or the lowest clinically effective dose, is usually equivalent to the lowest dose prescribed or recommended and takes into account the number of doses in a day. These values are derived from an assessment of the balance between efficacy and safety. The approach used to derive a screening value for drinking-water is to divide the MTD by a factor that would provide reasonable assurance that effects, either pharmacological or toxic, would be extremely unlikely. The derivation of this factor is based on expert judgement, as are the uncertainty factors used in the derivation of the ADI. The use of the MTD as a starting point for assessing potential risks of pharmaceuticals to human health or for deriving guideline values has been applied by Schwab et al. (2005) in a human health risk assessment of pharmaceuticals in surface waters in the USA and by Versteegh et al. (2007), Webb et al. (2003), van der Aa NGFM et al. (2009) and Bull et al. (2011). DWI (2007) also used the MTD as the basis for assessing the risk from pharmaceuticals in drinking-water.

The screening values developed are then used as reference points against which the results of monitoring can be judged. In some cases, because monitoring data are so limited, modelling has been used to develop worst-case estimates of potential exposure through water. The screening values are then used as the criteria to support decision-making when a chemical is detected in source water or drinking-water. If the concentration of a particular pharmaceutical exceeds the screening value, then further evaluations of the toxicity and occurrence of the pharmaceutical compound might be warranted. On the other hand, if the concentration is below the screening value, this strongly suggests that adverse health impacts should not be expected.

2.3 Applying the MTD approach: a Drinking Water Inspectorate study[1]

The Drinking Water Inspectorate for England and Wales commissioned a comprehensive desk-based review of current knowledge on and estimation of potential levels of 396 pharmaceuticals and 11 illegal drugs in drinking-water in the United Kingdom based on specific demographic and usage data on active pharmaceutical ingredients and using modelled concentrations based on actual catchments. The DWI (2007) approach was to determine an MOE for each pharmaceutical by comparing the MTD with the theoretical maximum intake from drinking-water.

The modelled concentrations from drinking-water intake were based on two methods: 1) a deterministic method that resulted in estimates of worst-case concentrations in drinking-water and 2) a probabilistic method that resulted in more realistic estimates

[1] This section is based on DWI (2007).

of the concentrations in drinking-water. Pharmaceuticals considered were first evaluated using the deterministic method; for those 24 compounds that had the lowest MOEs, further evaluation was done using the probabilistic method.

The health end-point used in this review was the MTD. Owing to insufficient data, an MTD value of 10 mg per day was used for topically applied pharmaceuticals and a conservative MTD value of 1 mg per day was used for pharmaceuticals for which there were no data, including illegal drugs. For the DWI (2007) evaluation, an uncertainty factor of 1000 was applied for all the compounds as a precautionary value to extrapolate below the level at which effects might be seen. The resultant screening values were used for determining the priority substances for further examination by probabilistic modelling. This additional uncertainty factor, which is widely accepted as a precautionary step by the medical profession, also provides an additional reassurance with regard to exposure of infants and young children.

The MOE for each of the targeted pharmaceuticals was derived by comparing the maximum estimated concentrations in drinking-water with the MTD. The results allow an assessment of the significance of individual pharmaceuticals through drinking-water exposure.

From the worst-case deterministic modelling, only 10 substances showed an MOE less than 1000, of which 4 were illegal drugs, with highly precautionary values for the lowest active dose. In only one case was the exposure ratio less than 100, and this was an unique case, as a combined total for all NSAIDs was used, but compared against the lowest individual MTD for any of the NSAIDs in the group. The results therefore suggested that even in this worst-case situation, there is no significant health risk from intake of pharmaceuticals via drinking-water.

When probabilistic modelling was used to obtain a more realistic estimate of concentrations in drinking-water, the estimated concentrations of all but one substance were significantly lower. The MOEs for all substances were significantly greater than 1000, and only tetrahydrocannabinol and oseltamivir carboxylate had an MOE less than 1000 (Table 4).

The DWI (2007) study led to the conclusion that majority of the pharmaceuticals had MOEs greater than 1000, suggesting a substantial margin of safety against potential adverse health impacts from exposure to trace concentrations of pharmaceuticals in drinking-water.

2.4 Applying the ADI approach

2.4.1 Awwa Research Foundation study[1]

The Awwa Research Foundation commissioned a study to provide critical information regarding the occurrence of and risk assessment for pharmaceuticals and potential endocrine disrupting chemicals (EDCs) in drinking-water. The study examined 62

[1] This section is based on Snyder et al. (2008).

Table 4. Probabilistic modelling data for the top 24 drugs from worst-case deterministic modelling

Drug name	Mean PEC_{dw} (µg/l)	MTD (mg)	MOE	Comments
Total NSAIDs	2.74	7.5	2 737	Combination of 19 anti-inflammatory drugs
Cannabis (tetrahydrocannabinol)	1.377	1	726	Illegal drug
Oseltamivir carboxylate (Tamiflu active metabolite)	107	52	486	Used under pandemic conditions
LSD	0.097	1	10 309	Illegal drug
Cocaine (methylbenzoylecgonine)	0.029	1	34 483	Illegal drug
Aminophylline	0.15	1	6 667	Smooth muscle relaxant
Beclometasone	0.005	0.05	10 000	Anti-asthmatic
Zidovudine	0.057	0.5	8 772	Antiviral
Ecstasy	0.487	1	2 053	Illegal drug
Acamprosate	0.435	1	2 299	Alcoholism treatment
Total statins	1.27	5	3 937	Cholesterol reduction
Nitroglycerine	0.035 4	0.15	4 234	Vasodilator
Heroin (diamorphine)	0.004 49	1	222 717	Illegal drug
Simvastatin	1.18	5	4 227	Cholesterol reduction
Codeine	0.015 7	20	1 277 139	Narcotic analgesic
Ramipril	0.153	1.25	8 177	Diuretic
Lisinopril	0.396	2.5	6 316	Angiotensin converting enzyme inhibitor
Methadone	0.082 2	1	12 173	Opioid agonist
Furosemide	1.74	20	11 507	Diuretic
Amphetamine	0.017 4	1	57 405	Illegal drug
Norethisterone	0.023 6	0.35	14 824	Progesterone derivative
Doxazosin	0.006 81	1	146 843	α-blocker
Bendroflumethiazide	0.275	2.5	9 094	Diuretic
Cyclosporin	0.000 8	2	2 500 000	Immunosuppression

LSD, lysergic acid diethylamide; PECdw, predicted concentration in drinking-water
Source: DWI (2007)

chemicals, including 20 pharmaceuticals and active metabolites, 26 potential EDCs, 5 steroid hormones and 11 phytoestrogens (natural estrogens from plants). The health value applied in this study was the ADI, and a conservative approach was taken in the process of developing the ADI values, as illustrated in Table 5.

In this study, the ADIs were converted to drinking-water equivalent levels (DWELs) in micrograms per litre (or parts per billion) based on assumptions of a 70 kg body weight in adults and consumption of 2 litres per day.

Table 5. Principles for deriving ADIs for compounds considered in this study

Category of analytes	Derivation of ADIs
Compounds that are not carcinogenic	Dividing the highest dose at which an effect was not observed (NOAEL) or the lowest dose at which an effect was observed (LOAEL) in animal or human toxicity studies by uncertainty factors to account for extrapolation to potentially sensitive populations
Compounds with positive evidence of carcinogenicity in high-dose animal studies and data on tumour incidence per dose level	A linear extrapolation model was used to predict the tumorigenic response at low dose level
Carcinogenic compounds with reported evidence in animal studies, but no available tumour incidence data	A safe dose corresponding to a cancer risk of one in a million was estimated

Even with the use of advanced and highly sensitive analytical procedures (with reporting limits in the nanograms per litre or parts per trillion range), none of the pharmaceuticals tested in this study were detected in finished drinking-water above the calculated health risk thresholds. Adopting a conservative worst-case scenario approach, the maximum detected concentrations in finished and piped drinking-water were used to calculate DWELs for each of the target pharmaceuticals. It was found that none of the pharmaceuticals detected in drinking-water exceeded their corresponding ADI.

The minimum margin of safety or MOE for each compound tested was calculated by dividing the DWEL by the maximum detected water concentration. According to United States Environmental Protection Agency (USEPA) policy, compounds with MOEs greater than 100 would generally indicate a low level of concern. Table 6 contains the calculated MOEs for some of the compounds that were detected in drinking-water; these were orders of magnitude above 100, suggesting a low level of concern.

Table 6. MOEs calculated for compounds considered in the Awwa Research Foundation study

Compound	MOE
Atenolol	2 700
Diazepam	110 000
Fluoxetine	41 000
Meprobamate	6 000
Norfluoxetine	44 000
Sulfamethoxazole	6 000 000
Triclosan	2 200 000

2.4.2 Australian Guidelines for Water Recycling[1]

The Australian Guidelines for Water Recycling were developed to serve as an authoritative reference for using recycled wastewater to augment drinking-water supplies. These guidelines were established to protect against microbial and chemical risks, including pharmaceuticals. The pharmaceuticals considered were categorized into two groups: those used solely for humans and those used for agricultural and veterinary purposes.

For veterinary pharmaceuticals, the health end-point is determined based on ADIs established for pharmaceuticals used for agricultural and veterinary purposes by organizations such as the Joint FAO/WHO Expert Committee on Food Additives, the Australian Therapeutic Goods Administration and the European Medicines Agency.

For human pharmaceuticals, the health end-point was a surrogate ADI, which was derived by dividing the lowest daily therapeutic dose by safety factors ranging from 1000 to 10 000. The use of the lowest daily therapeutic dose as a starting point for deriving guideline values or assessing risk has been adopted by others (Webb et al., 2003; Schwab et al., 2005; DWI, 2007; Versteegh et al., 2007; Bull et al., 2011). With respect to pharmaceutical metabolites in source waters, it was considered that the activity of metabolites is generally lower than that of the parent compound, and application of safety factors in the range of 1000–10 000 should provide a safety buffer that is sufficiently conservative.

For most pharmaceuticals, a safety factor of 1000 was applied to the lowest daily therapeutic dose; it consists of a 10-fold factor for sensitive humans, a 10-fold factor for infants and children and a 10-fold factor for the lowest therapeutic dose not being a no-effect level. In addition, a factor of 10 was added for cytotoxic drugs as a result of the higher toxicity associated with these compounds and for hormonally active steroids, which are active at very low concentrations and for which there is a high public perception of adverse effects.

In applying the guidelines, the calculated guideline values for the pharmaceuticals were compared with the highest concentrations measured in secondary treated effluent to derive the MOEs. Most of the calculated MOEs are more than 1000; given that this does not take into account reductions achieved by treatment processes, it is unlikely that pharmaceutical chemicals will be present at levels approaching the recommended guideline values or cause any adverse impacts on human health.

2.5 Conclusion

Risk assessments from the United Kingdom, the USA and Australia have applied the the ADI or the MTD approaches, in conjunction with uncertainty factors, to derive screening values for pharmaceuticals in drinking-water. Analysis of the results indicated that adverse human health impacts are very unlikely from exposure to the trace concentrations of pharmaceuticals that could potentially be found in treated drinking-water. Available data have shown that for those substances that have been

[1] This section is based on NRMMC, EPHC & NHMRC (2008).

detected, the concentrations are more than 1000-fold less than the MTD, which is the lowest clinically active dosage.

These findings are in line with other studies over the past decade that also supported the conclusion that discernible risks to health arising from trace levels of pharmaceuticals in drinking-water are extremely unlikely (e.g. Christensen, 1998; Schulman et al., 2002; Webb et al., 2003; Jones, Lester & Voulvoulis, 2005; Bercu et al., 2008; Snyder, 2010).

Given the low likelihood of human health risk, it is not considered necessary to implement routine monitoring programmes that are resource intensive and detract from other drinking-water concerns that are more important and more acute, particularly the threat of waterborne pathogens. However, where specific circumstances indicate a potential for elevated concentrations, screening values and targeted investigative monitoring could be considered.

Future research could consider investigating the robustness and feasibility of adapting the concept of the threshold of toxicological concern, which is currently more widely used for food additives and contaminants, as an alternative screening-level risk assessment, rather than developing values for each substance individually (Kroes et al., 2004). Research could also look into improvement to risk assessment methodology to address concerns related to pharmaceuticals mixtures and the effects of chronic, low-level exposure to pharmaceuticals, including exposure of sensitive subpopulations, such as pregnant women and patients with particular diseases and medical treatments (Rowney, Johnson & Williams, 2009). The WHO Framework for Risk Assessment of Combined Exposure to Multiple Chemicals (Meek et al., 2011) could be utilized to further consider the issue of mixtures.

3. Treatment technologies for removal of pharmaceuticals from water

3.1 Introduction

Many studies have reported the presence of pharmaceuticals in effluents from wastewater treatment facilities (Ternes, 1998; Andreozzi et al., 2003; Miao et al., 2004; Paxéus, 2004; Castiglioni et al., 2006; Vieno, Tuhkanen & Kronberg, 2007), and identified these effluents as the main conveyors of pharmaceuticals and their metabolites into receiving water sources, such as rivers, lakes, reservoirs and groundwater aquifers, that are used for drinking-water supply (Heberer, 2002; Ternes & Joss, 2006; Xu et al., 2007; Zhang, Geissen & Gal, 2008; Huerta-Fontela, Galceran & Ventura, 2011).

The presence of trace concentrations of pharmaceuticals in the water cycle, typically in the nanogram to low microgram per litre range, has raised questions concerning the efficacy of drinking-water and wastewater treatment processes in removing pharmaceuticals. The majority of research studies on treatment efficacy have been conducted in Europe and the USA, with some studies conducted in developed countries in Asia (Lee et al., 2008; Simazaki et al., 2008; Van De Steene, Stove & Lambert, 2010; Huerta-Fontela, Galceran & Ventura, 2011). In addition, there are more studies that focus on removal efficacies at laboratory scale or by single treatment processes rather than at full scale, especially for drinking-water treatment processes.

This chapter provides an overview of the removal of pharmaceuticals by conventional and advanced wastewater and drinking-water treatment processes based on the published literature.

3.2 Removal of pharmaceuticals by wastewater treatment processes

Conventional wastewater treatment facilities typically have biological degradation using the activated sludge process, whereas advanced facilities have tertiary treatment processes, such as reverse osmosis, ozonation and advanced oxidation technologies. Pharmaceuticals are a diverse group of chemicals, with varying physical and chemical properties (Jelic et al., 2011). Treatment efficacy depends on these physical and chemical characteristics (e.g. hydrophobicity), their reactivity towards different treatment processes and process control, such as solids retention time, temperature and hydraulic retention time. For example, the majority of pharmaceuticals are relatively hydrophobic and therefore less effectively removed by sorption to sludge (Vieno, Tuhkanen & Kronberg, 2007). Treatment removal efficiency could therefore vary significantly between different treatment facilities or at different time periods within the same treatment facility (Vieno, Tuhkanen & Kronberg, 2007).

Table 7 collates the results of several studies to illustrate the removal rates that can be expected by different wastewater treatment processes. These are based on observations of treatment processes ranging from single unit processes to full-scale wastewater treatment facilities found in the various studies.

Table 7. Conventional and advanced wastewater treatment processes and their expected range of removal efficiency for pharmaceuticals

Treatment process	Removal range (%)	Water source	Areas studied	Reference
Conventional wastewater treatment processes				
Activated sludge	11–99	Raw sewage	Australia	Watkinson, Murby & Costanzo (2007)
	7–100	Primary settled sewage	Europe, Japan	DWI (2007)
	< 20–80	Primary settled sewage	France	Gabet-Giraud et al. (2010)
	–193–86[a]	Primary settled sewage	Europe	Vieno, Tuhkanen & Kronberg (2007)
	8–98	Not specified	Brazil, Europe, Japan	Ziylan & Ince (2011)
Biological filtration	6–71	Primary settled sewage	Europe	DWI (2007)
Primary settling	3–45	Not specified	Brazil, Europe, Japan	Ziylan & Ince (2011)
Coagulation, filtration and settling	5–36	Not specified		
Sand filtration	0–99	Activated sludge effluent		
Advanced wastewater treatment processes				
Ozonation	1–99	Activated sludge effluent	Brazil, Europe, Japan	Ziylan & Ince (2011)
	86–100	Secondary effluent	France	Gabet-Giraud et al. (2010)
Ozonation/ ultrasound and sonocatalysis	23–45	Not specified	Europe, India, Japan, Turkey, USA	Ziylan & Ince (2011)
Ozonation and catalytic ozonation	>9–100			
UV irradiation	29	Not specified	Brazil, Europe, Japan	Ziylan & Ince (2011)
Photolysis (UV/ hydrogen peroxide)	52–100	Not specified	Europe, India, Japan, Turkey, USA	Ziylan & Ince (2011)
Dark and light Fenton	80–100			
UV/TiO_2	> 95			
Biomembrane	23–99	Treated effluent	Brazil, Europe, Japan	Ziylan & Ince (2011)
Microfiltration and reverse osmosis	91–100	Secondary treated effluent	Australia	Watkinson, Murby & Costanzo (2007)

Table 7 (contd)

Treatment process	Removal range (%)	Water source	Areas studied	Reference
Reverse osmosis	62–97	Secondary treated effluent	France	Gabet-Giraud et al. (2010)
Ultrasound	24–100	Not specified	Europe, India, Japan, Turkey, USA	Ziylan & Ince (2011)

UV, ultraviolet

[a] The removal of some pharmaceuticals appears to be negative. This has been attributed to the way in which removal is calculated, without hydraulic retention time being considered. This means that the effluent sample does not directly correspond to the influent sample. In the case of carbamazepine, the increase observed was consistent, and the most probable cause was reported to be conversion of carbamazepine glucuronides and other conjugated metabolites to the parent compound by enzymatic processes in the treatment plant (Ternes et al., 1999; Vieno, Tuhkanen & Kronberg, 2007).

Table 7 demonstrates that conventional wastewater treatment facilities with activated sludge processes can achieve higher removal efficiency than simple biological filters. Removal rates for pharmaceuticals can vary and could sometimes be limited (Kasprzyk-Hordern, Dinsdale & Guwy, 2009), depending on such factors as sludge age (DWI, 2007), activated sludge tank temperature and hydraulic retention time (Wick et al., 2009; Gabet-Giraud et al., 2010).

Advanced wastewater treatment processes, such as ozonation, membrane treatment and advanced oxidation, can generally achieve higher removal rates (up to 100%) for pharmaceuticals compared with conventional processes. For example, another bench-scale study showed that advanced oxidation processes can achieve up to 100% removal for diclofenac (Klavarioti, Mantzavinos & Kassinos, 2009).

Prediction of removal rates for wastewater treatment processes is possible for pharmaceuticals with very similar chemical structures. However, practical difficulties do exist in predicting removal rates between different wastewater treatment facilities, as highly variable removal rates are obtained for beta blockers, depending on the wastewater treatment facility under consideration. For example, the beta blockers betaxolol, bisprolol, carazolol and metprolol are significantly removed by activated sludge processes, with reported removal rates varying from 65% to about 90% (Ternes, 1998; Gabet-Giraud et al., 2010), whereas low removal rates of less than 20% and approximately 32% are reported for soltalol and propranolol, respectively, in other studies (Bendz et al., 2005; Gabet-Giraud et al., 2010).

3.3 Removal of pharmaceuticals by drinking-water treatment processes

Treated effluents from wastewater treatment facilities that have an impact on receiving water bodies constitute the main source of pharmaceuticals in surface waters, which could be used for drinking-water supply (Rahman, Yanful & Jasim, 2009). Other possible pathways of pharmaceuticals to drinking-water sources include leaching of pharmaceuticals to groundwater (Gomes & Lester, 2003) from sources such as leaking sewage systems and pipes.

None of the wide range of drinking-water treatment processes available have been designed specifically to remove pharmaceuticals that may be present in source waters. Nonetheless, removal of pharmaceuticals during drinking-water treatment is largely dependent on their physical and chemical properties, and treatment processes can therefore achieve some level of removal. For example, biodegradation on slow sand filters and/or sorption to particles removed by coagulation may help reduce the levels of some pharmaceuticals present in drinking-water sources; granular activated carbon (GAC) and powdered activated carbon (PAC) are increasingly adopted in drinking-water treatment to remove pesticides and improve taste and odour, and these processes may remove some pharmaceuticals by sorption (or biodegradation on GAC). Groundwater sources that are used for drinking-water typically have low particulate matter and organic matter content. Therefore, drinking-water treatment is mostly single-stage disinfection, without multiple treatment barriers.

Table 8 summarizes the findings in various published studies on the removal efficiencies of conventional and advanced water treatment processes for pharmaceuticals in drinking-water. The majority of these studies focused on bench-scale removal by spiking water samples with target compounds, subjecting these samples to treatment and measuring the resulting concentrations. However, some full-scale studies at drinking-water treatment facilities have been carried out.

Bench-scale studies using both alum and ferric chloride as coagulants for natural water or pure water samples spiked with pharmaceutical target compounds showed that coagulation (with or without chemical softening) is largely ineffective in removing pharmaceutical target compounds (Westerhoff et al., 2005; Yoon et al., 2006; Snyder et al., 2007). An Awwa Research Foundation project also concluded that coagulation was largely ineffective for pharmaceutical removal in bench-scale, pilot-scale and full-scale investigations (Khiari, 2007).

Chlorination and ozonation can achieve higher removal rates, with efficacy a function of chemical structure and treatment conditions, such as pH and oxidant dose (Zwiener & Frimmel, 2000; Adams et al., 2002; Huber et al., 2003, 2005; Snyder et al., 2003; Ternes et al., 2003; Pinkston & Sedlak, 2004; Kim et al., 2007). In some studies, free chlorine was found to oxidize approximately half of the pharmaceuticals investigated, but chloramine was comparatively less efficient. Antibiotics such as sulfamethoxazole, trimethroprim and erythromycin are among the compounds that showed high removal by free chlorine (Khiari, 2007). Advanced oxidation processes using ozone with hydrogen peroxide greatly improve oxidation and are frequently applied in wastewater recycling processes for indirect potable reuse to convert recalcitrant organic chemicals.

PAC and GAC can achieve high removal of pharmaceutical target compounds, especially hydrophobic compounds. Removal efficacy is a function of contact time, organic loading, chemical structure, solubility and carbon type (Ternes et al., 2002; Yoon Y. et al., 2003; Snyder et al., 2006). Iopromide, ibuprofen, meprobamate, sulfamethoxazole and diclofenac were some of the compounds found to be most resistant to activated carbon removal (Khiari, 2007).

Table 8. Drinking-water treatment processes and their expected range of removal of pharmaceuticals

Treatment process	Removal range (%)	Scale	Country studied (no. of compounds)	Reference
RO	> 99	Pilot	Germany (6)	Heberer, Reddersen & Mechlinski (2002)
RO1	70–91	Bench	Japan (6)	Kimura et al. (2004)
RO2	10–85	Bench		
UV/H_2O_2	3 – > 95	Bench	USA (2)	Rosenfeldt & Linden (2004)
Coag	24–72	Bench	USA (49)	Westerhoff et al. (2005)
PAC (20 mg/l)	> 80	Bench		
PAC (1 mg/l)	40–75	Bench		
Cl_2	25–75	Bench		
O_3	5–95	Bench		
O_3	33–100	Bench	Germany (9)	McDowell et al. (2005)
ClO_2	0–100	Bench	Germany (11)	Huber et al. (2005)
NF1	> 98	Bench	Australia (3)	Nghiem, Schäfer & Elimelech (2005)
NF2	> 80	Bench		
UF	< 30	Bench	USA (27)	Yoon et al. (2006)
NF	30–90	Bench		
Coag	< 5–30	Bench	Finland (5)	Vieno, Tuhkanen & Kronberg (2006)
Cl_2	20–100	Bench	Japan (9)	Simazaki et al. (2008)
PAC	> 98	Bench		
Coag	< 15	Bench		
Constructed wetlands	28–60	Pilot	Singapore (4)	Zhang et al. (2011)
Aeration/SF	25 – > 95	Full	Germany (5)	Reddersen, Heberer & Dünnbier (2002)
O_3/Coag/Sed/Cl_2	100	Full	USA (2)	Boyd et al. (2003)
PAC/Coag/Sed	0	Full	USA (1)	
Cl_2	100	Full	USA (1)	
Coag	0	Full	Republic of Korea (6)	Kim et al. (2007)
UF	0	Full		
GAC	100	Full		
NF	30– > 90	Full	Spain (12)	Radjenović et al. (2008)
RO	45– > 90	Full		
Disinfection	2–97	Full	France (7)[a]	ANSES (2011)
Physical and chemical	31–94	Full		
O_3 + AC	47–97	Full		
Membranes	6–68	Full		
Pre-Cl_2	0 – > 99	Full	Spain (35)	Huerta-Fontela, Galceran & Ventura (2011)
Coag/Floc/SF	< 30–100	Full		
O_3	5 – > 99	Full		

Table 8 (contd)

Treatment process	Removal range (%)	Scale	Country studied (no. of compounds)	Reference
GAC	55 – > 75	Full		
Cl_2	14–100	Full		

AC; activated carbon, Cl_2, chlorine; ClO_2, chlorine dioxide; Coag, coagulation; Floc, flocculation; GAC, granular activated carbon; H_2O_2, hydrogen peroxide; NF, nanofiltration; O_3, ozonation; PAC, powdered activated carbon; RO, reverse osmosis; Sed, sedimentation; SF, sand filtration; UF, ultrafiltration; UV, ultraviolet

[a] Note that this was a national study incorporating 78 instances of pharmaceutical removal.

Membrane treatment is highly effective in removing chemicals from water, and removal efficacy is a function of physical and chemical properties, such as molecular weight, hydrophobicity, polarity, chemical nature and pore size of the membranes. Some studies (Yoon et al., 2006; Khiari, 2007) suggested that nanofiltration (NF) can achieve better removal rates for most target compounds than ultrafiltration (UF)/microfiltration (MF) membranes as a result of both hydrophobic adsorption and size exclusion. Higher molecular weight substances would be removed by size exclusion, especially by NF membranes. Reverse osmosis (RO) was highly effective, despite trace quantities of some target compounds breaching RO membranes. However, a double-pass RO system was reported to remove all target compounds to below detection limits (Khiari, 2007).

Ultraviolet (UV) irradiation at typical disinfection dosages was ineffective for removing most target compounds, even though it can achieve more than 50% removal of sulfamethoxazole (antibiotic), triclosan (antimicrobial) and diclofenac (NSAID). However, a combination of higher-dose UV (400 mJ/cm^2 and higher) with hydrogen peroxide (3 mg/l and above) removed most target compounds (Rosenfeldt & Linden, 2004; Khiari, 2007).

3.4 Conclusion

This chapter has provided an overview of the removal of pharmaceuticals by conventional and advanced wastewater and drinking-water treatment processes based on the published literature.

Conventional wastewater treatment typically consists of activated sludge processes. Biological treatment, such as activated sludge and biofiltration, has demonstrated significant removal rates for pharmaceuticals that are biodegradable or readily bind to particles (Ternes et al., 1999; Joss et al., 2005; Kim et al., 2007). However, removal rates for pharmaceuticals can vary within and between studies (Kasprzyk-Hordern, Dinsdale & Guwy, 2009; Wick et al., 2009), depending on such factors as sludge age (DWI, 2007), activated sludge tank temperature and hydraulic retention time. For example, diclofenac removal in the activated sludge process ranges from 21% to 50%, but this can be optimized by operating the process at a sludge age of eight days or more (Ziylan & Ince, 2011).

Advanced wastewater treatment processes that comprise membranes, advanced oxidation technologies, etc. have shown higher removal efficiencies for pharmaceuticals (e.g. advanced oxidation processes can achieve up to 100% removal

for diclofenac) (Klavarioti, Mantzavinos & Kassinos, 2009). However, conventional treatment is generally sufficient to meet regulatory requirements, and capital-intensive advanced treatment processes are not commonly adopted for wastewater treatment (Spellman, 2010).

With respect to conventional drinking-water treatment, bench-scale studies showed that coagulation (with or without chemical softening) is largely ineffective in removing pharmaceuticals (Westerhoff et al., 2005; Yoon et al., 2006; Snyder et al., 2007). Free chlorine was found to oxidize approximately half of the pharmaceuticals investigated, and chloramine was less efficient. Antibiotics such as sulfamethoxazole, trimethroprim and erythromycin are among the compounds that showed high removal by free chlorine (Khiari, 2007).

Advanced water treatment processes such as ozonation, advanced oxidation, activated carbon and membrane processes (nanofiltration, reverse osmosis) were demonstrated to achieve higher removal rates (above 99%) for targeted pharmaceutical compounds in various published literature studies. However, advanced oxidation processes can lead to incomplete degradation products, such as metabolites, and future research could consider the value and feasibility of studying the formation and impact of these metabolites (Celiz, Tso & Aga, 2009).

For drinking-water sources that are contaminated with pesticides, advanced treatment may already be in place to meet regulations. In such cases, removal of pharmaceuticals during treatment may already be optimized.

Most importantly, it is prudent to note that advanced and costly water treatment technology will not be able to completely remove all micropollutants to concentrations below the detection limits of the most sensitive analytical procedures at all times. Therefore, it is imperative to consider the toxicological relevance of various compounds in the context of appreciable risks to human health. Increased or rapidly changing exposure arising from specific local circumstances (e.g. a significant increase in the concentration of pharmaceuticals in surface waters impacted by wastewater discharge) should be investigated.

An informed risk assessment considering the above principles is essential before allocating scarce resources to upgrade or invest in additional advanced treatment processes to reduce trace concentrations of pharmaceuticals in drinking-water.

In view of the substantial margin of safety for consumption of very low concentrations of pharmaceuticals in drinking-water (Chapter 2 in this report), concerns over pharmaceuticals should not divert the attention and resources of water suppliers and regulators from other chemical and pathogenic microbial priorities. For example, although the government in Australia has issued proposed guideline values for 84 pharmaceuticals for water reuse schemes, but microbial pathogens remain their overriding priority in water reuse (NRMMC, EPHC & NHMRC, 2008).

4. Preventing pharmaceuticals in drinking-water

Conventional drinking-water quality monitoring that places emphasis on end-product testing is very resource intensive in terms of capital investment and human resources. With an expanding list of chemical contaminants detected in drinking-water and water sources that may be of insignificant health concern, an overemphasis on end-product monitoring and the upgrading of treatment infrastructure is clearly not sustainable or an optimal use of limited resources.

Chapter 4 in the fourth edition of the WHO *Guidelines for Drinking-water Quality* states that the water safety plan is "the most effective means of consistently ensuring the safety of a drinking-water supply … through the use of a comprehensive risk assessment and risk management approach that encompasses all steps in the water supply from catchment to consumer" (WHO, 2011). The key principles of water safety plans underline the importance of looking at risk assessment and risk management across the entire water cycle starting at source. Adapting this full life cycle approach to pharmaceuticals in drinking-water means that preventing pharmaceuticals entering the environment during their production, consumption and disposal is a pragmatic and effective means of risk management.

Inappropriate disposal practices, such as flushing unwanted or excess drugs down toilets and sinks and discarding them in household waste, are common and often a significant contributor of pharmaceuticals present in wastewater and other environmental media (e.g. surface waters and landfill leachate). A survey from Germany's Management Strategies for Pharmaceutical Residues in Drinking Water research programme showed that consumers discarded 23% of liquid pharmaceuticals prescribed and 7% of tablets. While some went into household trash, the equivalent amount of pharmaceuticals that was flushed away is approximately 364 tons every year (Lubick N, 2010). Another survey of households in the United Kingdom in 2003 found that 63% of unwanted pharmaceuticals were discarded in household waste and 11.5% were flushed down sinks or toilets (Bound & Voulvoulis, 2005). Similarly, proper and well-managed disposal practices at concentrated point sources such as health-care and veterinary facilities will help mitigate the entry of pharmaceuticals into our environment.

Currently, tighter rules and regulations apply to controlled substances and cytotoxic drugs than for other pharmaceuticals. Despite this, disposal to sewers is not precluded (USEPA, 2008a). Disposal of non-controlled substances tends to be more variable and is often developed on a local, jurisdictional or regional basis. A scan of the current literature, which is not exhaustive, revealed a few broadly categorized preventive measures in Australia, Canada, the USA and European countries that could potentially reduce the entry of pharmaceuticals into our environment. These measures are described below.

4.1 Improved regulations and guidance on pharmaceutical waste management

All health-care facilities should have policies and procedures in place for the correct management of pharmaceutical waste. In Australia, the Environmental Protection Authority and the National Health and Medical Research Council had guidelines on

the management of waste generated in health-care facilities. The National Health and Medical Research Council stated that, where possible, pharmaceutical waste should be incinerated and should not be sent to landfills or discharged to sewers (NHMRC, 1999). Licensed waste disposal companies collected all clinical and pharmaceutical waste for disposal in authorized waste disposal facilities.

In the USA, frequently used pharmaceuticals, such as epinephrine, warfarin and selected chemotherapeutic agents, are regulated as hazardous waste under the Resource Conservation and Recovery Act. Failure to comply with the regulations under this Act through improper management and disposal of waste can potentially constitute serious violations and incur heavy penalties. To guide stakeholders on acceptable disposal practices, the USEPA supported the development of *Managing Pharmaceutical Waste: A 10-Step Blueprint for Health Care Facilities in the United States*, which recommends a stepwise approach to help health-care facilities develop and implement a comprehensive pharmaceutical hazardous waste management programme. This blueprint adopts the best practices in waste minimization to meet regulatory compliance for pharmaceutical waste disposal and safeguard human health and the environment in a cost-effective manner (Pines & Smith, 2006).

To this end, the USEPA (2010b) has also drafted a guidance document, *Best Management Practices for Unused Pharmaceuticals at Health Care Facilities*, to advise health-care and veterinary facilities on reducing pharmaceutical waste, on pharmaceutical waste management and on application of disposal regulations. The aim is to help reduce the amount of pharmaceuticals that are discharged to water bodies.

4.2 Pharmaceutical take-back programmes

To augment regulations, take-back programmes have been established by government and private organizations in several countries to reduce the amount of drugs entering our environment (Daughton, 2003, 2004; Glassmeyer et al., 2009; Teleosis Institute, 2009). A survey of households in the United Kingdom in 2003 showed that 22% of excess pharmaceuticals were returned to pharmacists; although take-back programmes were effective, further improvement is needed (Bound & Voulvoulis, 2005).

These programmes can be of different scales, ranging from small one-day collection events to regular and systematic regional collection, ongoing return of unused and excess medicines to participating pharmacies and mail-back programmes where excess medicines are returned in prepaid packs to government-supervised mailboxes (SCBWMI, 2005). Several household hazardous waste collection programmes have also added pharmaceuticals to the list over the years (Glassmeyer et al., 2009).

In Australia, the Commonwealth Department of Health & Ageing Services provided funds to establish a system for the collection and disposal of unwanted medicines, known as the Return Unwanted Medicines (RUM) Project. Estimates from RUM showed that in 2010–2011, more than 34 tonnes of unwanted medicines on average are collected monthly by community pharmacies across Australia and subsequently incinerated according to guidelines (RUM, 2011).

In the USA, many scheduled pharmaceutical collection events facilitate prudent disposal of unwanted medications at the regional level, such as the successful "Great Lakes Earth Day Challenge", which collected 4.5 million pills for safe disposal. The USEPA has also awarded grants to support take-back of non-controlled, unused medicines at pharmacies and mail-back of unused medicines with appropriate involvement of law enforcement (USEPA, 2010a). Other mechanisms to reduce the entry of pharmaceuticals into the environment include establishing best management practices for handling solid wastes and minimizing discharge from landfills.

Canada has formal stewardship programmes for household pharmaceutical waste at the provincial level or in cities that provide convenient options for consumers to return pharmaceuticals to community pharmacies for safe disposal.

Europe has widespread standardized take-back programmes. In the 2010 report *Pharmaceuticals in the Environment: Results of an EEA Workshop*, the European Environment Agency (EEA, 2010) stated that most countries in Europe collect unused drugs separately from household waste, usually at pharmacies (a handful also have separate collection sites alongside pharmacies). The national systems are operated and funded by the pharmaceuticals industry, retail pharmacies or the public sector. The operation of the take-back programmes may be the responsibility of the retail pharmacies or of public or private waste contractors (Teleosis Institute, 2009).

4.3 Raising consumer awareness

Consumers are accustomed to disposing of unwanted and expired medicines through household waste and sewers. Such improper disposal practices release pharmaceuticals into our environment, wastewater and water sources. There is therefore a need to raise public awareness and encourage consumers to adopt proper disposal practices for unwanted pharmaceuticals. In Australia, the RUM Project focuses on raising consumer awareness to inform consumers of the appropriate option for drug disposal (RUM, 2010). In addition to regulations under New York's Drug Management and Disposal Act, the New York State Department of Environmental Conservation publishes posters for all pharmacies and retail stores that sell drugs to advise consumers on the proper storage and disposal of unwanted medication (DEC, 2010). Consumers can then serve as environmental stewards to reduce water pollution.

4.4 Conclusion

Appropriate regulations governing disposal practices at point sources of hazards, widespread take-back programmes, guidance and enhanced consumer education will support efforts for the proper disposal of unwanted and excess medicines and reduce the environmental impact of pharmaceuticals entering our environment, including water sources.

As most pharmaceuticals enter the water cycle through wastewater discharges or from poorly controlled manufacturing or production facilities that are primarily associated with generic medicines, the discharge of untreated or poorly treated wastewater to water bodies used as drinking-water sources should be strongly discouraged.

5. Conclusions, recommendations and knowledge gaps

Pharmaceuticals are synthetic or natural chemicals that can be found in prescription medicines, over-the-counter therapeutic drugs and veterinary drugs. They contain active ingredients that are designed to achieve pharmacological effects and confer significant benefits to society. Pharmaceuticals are primarily introduced into the environment via human excretion, sewage effluent, improper drug disposal, agricultural runoff, and livestock and veterinary waste. The ubiquitous use of pharmaceuticals in various settings has resulted in a continuous discharge of pharmaceuticals and metabolites into the environment, leading to their "pseudo-persistence" in the environment. Significant advancements in the sensitivity of detection and analytical technologies and methods have made it possible to detect very low concentrations of pharmaceuticals in the range of nanograms to low micrograms per litre in the water cycle. As pharmaceuticals contain active ingredients that are designed to achieve specific pharmacological effects based on their biological reactivity and biochemical properties, their presence at trace concentrations in the water cycle has generated concerns among various stakeholders, including governments, regulators and the public, over potential risks to human health through very low level exposure via drinking-water.

5.1 Conclusions

Targeted investigative studies conducted in the United Kingdom, the USA and Australia have shown that concentrations of pharmaceuticals in surface water and groundwater sources impacted by wastewater discharges are typically less than 0.1 µg/l (or 100 ng/l). Detection in treated drinking-water is rare; if pharmaceuticals are present, their concentrations are usually well below 0.05 µg/l (or 50 ng/l). There are, however, very few systematic monitoring programmes or comprehensive, systematic studies on the occurrence of pharmaceuticals in drinking-water, and limited occurrence data present one of the key challenges in assessing the potential risks associated with trace concentrations of pharmaceuticals in drinking-water.

Nonetheless, several approaches to screen and prioritize pharmaceuticals have been published in the peer-reviewed literature. MTDs, ADIs and sometimes the DWELs have been used as reference values by which to derive a margin of safety between these and the reported or predicted worst-case exposure in drinking-water.

Targeted investigations conducted in the above-mentioned countries found that traces of pharmaceuticals in drinking-water are largely present at several orders of magnitude (more than 1000-fold) below the lowest therapeutic dose and largely below the calculated ADIs. The substantial margins of safety for individual compounds suggest that appreciable adverse impacts on human health are very unlikely at current levels of exposure in drinking-water.

From a treatment perspective, pharmaceuticals are not unusual organic chemicals, and treatment removal rates are reasonably predictable based upon the physical and chemical properties of the compounds. Conventional treatment processes with coagulation, filtration and chlorination can remove about 50% of these compounds, whereas advanced treatment, such as ozonation, advanced oxidation, activated carbon and membrane processes (e.g. reverse osmosis, nanofiltration), can achieve higher

removal rates; reverse osmosis, for example, can remove more than 99% of large pharmaceutical molecules.

5.2 Recommendations

The substantial margin of safety for consumption of very low concentrations of pharmaceuticals in drinking-water suggests that appreciable adverse impacts on human health are very unlikely. As such, concerns over pharmaceuticals should not divert attention and valuable resources of water suppliers and regulators from other priorities, such as pathogenic microbial water quality issues. The low risk to human health from current levels of exposure in drinking-water suggests that development of formal guideline values for pharmaceuticals in the WHO *Guidelines for Drinking-water Quality* and the installation of specialized treatment processes to reduce trace concentrations of pharmaceuticals are not warranted.

Routine monitoring programmes for pharmaceuticals in water sources and drinking-water and additional or specialized drinking-water treatment to reduce very low concentrations of pharmaceuticals in drinking-water are not deemed necessary due to the limited public health benefits. However, where local circumstances, such as a catchment survey, indicate a potential for elevated levels of pharmaceuticals in the water cycle (surface water, groundwater, wastewater effluent and drinking-water), relevant stakeholders could undertake targeted, well-designed and quality-controlled investigative studies to obtain more information with which to assess the potential health risks arising from exposure through drinking-water. If necessary, screening values could be developed based on the MTD or the ADI approaches, and an assessment of the need for treatment enhancement could also be considered within the context of other risks and priorities using water safety plans.

Reduction of human exposure to pharmaceuticals through drinking-water can be achieved through a combination of preventive measures, such as take-back programmes, regulations, public guidance and consumer education to encourage the proper disposal of unwanted pharmaceuticals and minimize the introduction of pharmaceuticals into the environment. It is also imperative to enhance public communication and education on water quality issues from the human health standpoint. For example, conveying to the public the potential health risks from exposure to very low concentrations of pharmaceuticals in drinking-water will help them to better understand this issue relative to other hazards, such as waterborne pathogenic microorganisms. However, in the long term, improvement of wastewater treatment to more efficiently remove a range of organic substances that are seen as emerging contaminants of concern would provide a more sustainable and comprehensive solution in preventing their entry into the water environment.

5.3 Knowledge gaps and future research

Although current risk assessments indicate that very low concentrations of pharmaceuticals in drinking-water are very unlikely to pose any risks to human health, there are knowledge gaps in terms of assessing the risks associated with long-term, low-level exposures to pharmaceuticals and possible combined effects of chemical mixtures, including pharmaceuticals. Future research investigating the possible additive or synergistic effects of mixtures would be beneficial for an accurate

exposure assessment to determine whether there are any potential risks to human health, taking into account sensitive subpopulations.

One of the key challenges in estimating exposures to pharmaceuticals in drinking-water and assessing the potential risks to human health is the limited occurrence data for the diverse group of human and veterinary pharmaceuticals in use today. Implementing monitoring programmes is resource intensive in terms of costs, human resources and infrastructure, and there is also a lack of standardized sampling and analysis protocols to support monitoring studies. As such, future research looking into cost-effective methods to prioritize pharmaceuticals within the context of an overall risk assessment will benefit our appreciation of low levels of pharmaceuticals in drinking-water from a human health perspective.

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